

EVIDENCE OF CURE IN EXPERIMENTAL SYPHILIS

EVIDENCE OF CURE IN EXPERIMENTAL SYPHILIS WHEN USED FOR EVALUATION OF CHEMOTHERAPEUTIC PREPARATIONS

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Experimental rabbit syphilis has proved invaluable repeatedly not only for a better understanding of the syphilitic process but also for the evaluation of compounds used in the prophylaxis and treatment of the disease in human beings. Recently, for example, comparative examinations of the effects of Mapharsen and neoarsphenamine [A. L. Tatum and G. A. Cooper (1934), G. W. Raiziss and M. Severac (1935), B. J. Longley, N. M. Clausen and A. L. Tatum (1941), J. A. Kolmer and A. M. Rule (1941)] as well as various schemes of treatment [Kolmer and Rule (1941), H. Eagle and R. B. Hogan (1942)] have been carried out on syphilitic rabbits.

It follows that details of the procedure by which the therapeutic efficiency of drugs is evaluated in experimental syphilis are not merely of academic interest but of the greatest practical importance for the management of the disease in human beings.

Methods of transfer

Of the two main methods by which cure is determined in treated syphilitic rabbits, namely attempted reinfection of the treated animals and transfer of their tissues to other animals with negative results, the method of reinfection is too unreliable, and the majority of workers have adopted the tissue transfer method.

The latter method, however, has its weak points, and to the problem of eliminating them a further communication has recently been made by H. Eagle, R. B. Hogan and J. E. Kemp (1942) in a paper entitled "The Importance of the Time Factor in the Evaluation of 'Cure' in Syphilitic Rabbits." The authors have arrived at a conclusion similar to that of R. Prigge (1928), that premature transfer of tissue to another animal from one that has been treated for syphilis may by its negative result lead to a false conclusion as to cure since a transfer from the same animal some time later may be positive. In Eagle, Hogan and Kemp's animals transfer of lymph gland material from a syphilitic rabbit six weeks after treatment with 25 to 75 per cent of the curative dose was negative in a high percentage of cases although a later transfer, six months after the completion of treatment, was positive, proving that inferences of cure from the earlier transfers of the animals would have been false. The conclusion made by Eagle, Hogan and Kemp as to the fallibility of premature transfer of tissue from treated animals is all to the good in consolidating what has been established already on good evidence. Some points, however, in their article seem to call for comment. They concern the sufficiency or otherwise of lymph glands as the transfer material and the actual length of the interval not only between treatment and the transfer, but also that between inoculation and treatment.

Eagle, Hogan and Kemp begin their paper by saying, "Since the finding . . . that the lymph nodes of untreated syphilitic rabbits remain infectious for years, often in the absence of other demonstrable evidence of syphilitic infection, the result of a lymph gland transfer to a normal rabbit has been the *ultimate* (my italics) criterion in the experimental disease." They then refer to papers by A. M. Chesney and J. E. Kemp (1924 ; 1925) and continue, "If, e.g. the emulsified popliteal node of a treated syphilitic rabbit, injected intratesticularly or subscrotally into a normal animal, failed to cause the appearance of a dark-field positive lesion at the site of inoculation, the parent animal was adjudged cured."

Lymph gland transfer

Although Eagle, Hogan and Kemp mention that several papers have enjoined caution in the interpretation of lymph gland transfer they refer to only two of them, one by W. Worms (1926), the validity of whose conclusions they seem to

question (this will be discussed later), and the other by R. Prigge (1928). They convey the impression that transfer of lymph gland material is universally regarded as sufficient. Such an impression is erroneous as will be shown below.

Even Chesney and Kemp, whose work is referred to by Eagle, Hogan and Kemp, have at different times been cautious in their judgment of the above method. Thus they said (1924) that while arsphenamine causes disappearance of *Spirochaeta pallida* from lymph glands it is possible that they might still be present in less accessible tissues or appear again at a later date in the lymph glands. Further, although in 1924 and 1925 they expressed the belief that the most satisfactory method of evaluating antisyphilitic remedies in experimental syphilis was by lymph gland transfer or by transfer of internal organs supplemented by careful observation of treated animals over a considerable period of time, they asked (1925) "to what extent can the sterility of lymph nodes be regarded as an index of cure?" They admitted that they had made too few experiments to permit of generalization on the point and, in fact, the number of their treated animals examined by separate transfer of heart blood, heart muscle, liver, mixed spleen and bone marrow, testicle, brain and popliteal lymph gland was only six. Among the six treated animals which gave the above negative transfer results was one suffering from syphilitic keratitis which caused Chesney and Kemp to write: "it would appear from this observation that sterility of lymph nodes does not in every instance indicate that the animal is free of syphilitic infection, particularly if there has been a pre-existing keratitis. Lymph node sterility is, therefore, no absolute indication of cure of syphilis, and perhaps the same may be said of the internal organs, but is probably the best single index that we have."

Worms (1926) showed that lymph gland transfer from a treated rabbit could be misleading by giving rise to a latent infection ("nuller") only. The infection in this latent case was proved by transfer of a lymph gland from the rabbit to another (so-called "second passage") in which it produced a primary syphilitic lesion. P. Manteufel and W. Worms (1927) stressed the fact that destruction of the spirochaetes in the lymph glands was not conclusive evidence of sterilization of the animal, and P. Uhlenhuth and H. Grossmann (1927^{1, 2, 3}) believed that inoculation of a series of animals with an emulsion of liver, spleen and bone marrow and of more animals with an emulsion of several lymph glands followed by second passages of lymph glands from the animals was more reliable evidence of cure than the mere transfer of popliteal glands.

Modified methods of tissue transfer

C. Voegtlin and H. A. Dyer (1927) recommended a modified method of tissue transfer as trustworthy. In the firm belief that lymph gland transfer alone was not reliable, they inoculated one testicle of each of two rabbits with a suspension of two popliteal glands and the other testicle with an emulsion of the testicle of the treated animal; in addition they prescribed observation of the transfer animals for twelve weeks or longer, and, as an additional precaution, reinoculation of those rabbits which had not shown any signs of infection with a heavy suspension of spirochaetes, in order to exclude the possibility of a natural refractoriness of the transfer animals.

W. Kolle (1927), R. Prigge (1929) and W. Kolle and R. Prigge (1932) expressed the opinion that negative lymph gland or organ transfer does not permit the conclusion that the treated animals were sterilized.

W. H. Brown (1930) admitted that "despite the fact that emulsions prepared from all available parts of the body of treated animals have been injected into normal animals with negative results" *S. pallida* might still be present in "the skin, gastro-intestinal tract, or some other part of the body which cannot be used for injection without employing some method of sterilization which would invalidate the results". He further referred to the decreased number of the lowered virulence of *S. pallida* which might in itself be detrimental to the establishment of an infection by the transferred tissue. In spite of such a possibility Brown adopted a somewhat resigned attitude and admitted that "no more could be said about the

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absence or presence of an infection in a disease than that *it is or is not demonstrable* by the use of available methods"; and that "when the question has been narrowed down to the point of an undemonstrable infection, it has been carried sufficiently far for all practical purposes".

H. Schlossberger and W. Worms (1932), whilst admitting that even negative transfers of lymph glands and of organs, even with second passages, are not conclusive evidence of sterilization of the treated animals, raised the objection that Brown's views on the matter were not justified because the examination of a chemotherapeutic preparation in experimental syphilis is intended to serve as a guide to its use in the treatment of human syphilis. It is undoubtedly possible that a few *S. pallida* remaining in the animal, in spite of negative results of tests, may later be the starting point of a recurrence of the disease. T. F. Probey (1933) checked the result of his arsphenamine treatment of rabbits, which had been given two months after the inoculation, by transferring the originally inoculated testicle into one testicle, and the lymph glands into the other testicle of each of a number of healthy rabbits three months after treatment. J. von Vársárhelyi (1937) tried to answer the question, whether or not his rabbits had been sterilized through his treatment, by transferring separately emulsions of brain, testes, liver, spleen, inguinal and popliteal lymph glands into the testes of rabbits 85 to 119 days after treatment. F. Jahnelt (1938) in testing the effect of rhodium chloride and of sodium rhodium chloride on experimental rabbit syphilis used the method of the transfer of popliteal and inguinal glands and of testes, liver and spleen instead of only a single gland.

The above quotations show that the validity of lymph gland transfer alone has not been generally recognized as a safe procedure for the evaluation of chemotherapeutic preparations, although many investigators, and among them Eagle, Hogan and Kemp in their recent work, have apparently relied on it.

Experimental syphilitic work in mice

It is surprising that these experiments have been made so little use of in experimental syphilitic work in mice. It was H. Schlossberger (1930) who recommended the mouse as a very suitable animal for chemotherapeutic testing because *S. pallida*, invading the lymph glands and organs first, did not reach the brain for at least a fortnight after the inoculation; thus an opportunity was given to see if a chemotherapeutic agent was able to prevent or to cure the infection of the central nervous system. It may be mentioned here that such experiments in rabbits were not in the same and regular way possible as *S. pallida* only enters the central nervous system of these animals in exceptional instances. H. Schlossberger's experiments (1928) on the other hand showed that the passage of a *S. pallida* strain from rabbits through the brain of mice enabled the spirochaetes, when retransferred to rabbits, to invade the central nervous system of the latter. These results have been confirmed by G. W. Raiziss and M. Severac (1932) who (1933) were able to test chemotherapeutic preparations also in their effect on *S. pallida* in the brains of rabbits.

In 1931 and in 1937 Schlossberger reported further on the use of syphilitic mice in chemotherapeutic testing. The effect of treatment was established by subscrotal transfer of axillary and inguinal glands into one rabbit and of each half of the brain into two rabbits. Schlossberger showed that it was relatively easier to sterilize these animals with various preparations in the early stage of infection, that is five to six days after the inoculation, than when the treatment had been postponed to six to eight weeks. Thus, apparently, it was possible to sterilize the syphilitic mouse with 1/150 gramme Neosalvarsan per 20 grammes of mouse body weight (the tolerated dose of preparation is 1/135 gramme per 20 grammes of mouse body weight), with regular success, only if it was given in the early stage. On the other hand sterilizations of mice in the early and late stage of the infection were obtainable with some arseno-pyridine preparations which failed to show a corresponding effect in the treatment of the syphilitic rabbit. Schlossberger believed that apart from a possible different distribution and excretion of the chemo-

therapeutic preparation in the mouse such a discrepancy might be due to the comparatively smaller quantity of *S. pallida* in its body. Schlossberger considered that the smallness of the mouse gave it great advantages over the rabbit for chemo-therapeutic tests because its whole organs could be transferred into rabbits, a procedure which is impossible if the remedies are tested on syphilitic rabbits (P. Uhlenhuth and H. Grossmann, 1927²). Also A. M. Chesney (1930) being "well aware that it is difficult to prove that syphilis does not exist in a treated animal (rabbit)", and that the methods we now employ have their limitations and may prove faulty in the future declared "after all, one cannot grind up an entire rabbit and inoculate all of it into another rabbit." Jahnel (1938) also expressed a preference for using mice in such experiments because of the small size of their organs.

Emulsions of whole organs

In order to avoid the fallacy resulting from uneven distribution of the spirochaetes in the rabbit's tissues it is preferable to use thoroughly well mixed emulsions of whole organs, rather than emulsions of portions of organs as used, apparently, by A. M. Chesney and J. E. Kemp (1925). According to an experience of my own (1927) the distribution of *S. pallida* in the lymph glands is not uniform. In five untreated rabbits in the latent stage and in a sixth which was a "nuller" which I tested with the above in mind I found all the inguinal lymph glands infectious, four out of five of the popliteal, and three out of six of the axillary. Although in further experiments of mine (1928) the lymph glands and internal organs of rabbits treated in the latent stage of the infection gave uniformly negative results, even in second passages, a few positive results as those shown in my experiments on untreated rabbits are of more significance than many negative ones; also it should be noted that in the treated animals the transfer took place fifty-two to eighty-two days after the last of three weekly doses of 0.1 gramme of Neosalvarsan per kilo of body weight. In this connexion I refer to two rabbits in the experiments of F. Breinl and R. Wagner (1929). These animals had been inoculated thirty-nine days after the second of two intravenous injections of 0.1 gramme of Neosalvarsan per kilo of body weight and were killed forty-five and ninety-four days respectively after the inoculation. Their lymph glands and organ emulsions were then transferred separately into healthy rabbits. In both cases the emulsions of liver, spleen and bone marrow were negative, and only a part of their lymph glands gave positive results; unfortunately the negative ones were not checked by second transfer passages. Although second passages were not used in von Vászárhelyi's experiments (1937) mentioned above, his results of tissue transfers carried out 86 to 119 days after treatment of seventeen rabbits are very remarkable. The author obtained sixteen positive results out of seventeen with liver, thirteen out of sixteen with spleen, one out of fifteen with brain, and eleven out of sixteen with popliteal glands; there were, therefore, five first passage negative lymph gland transfers!

The experiments cited above show that it is unsafe to rely for the criterion of cure on results of transfer of a single tissue and that one must use emulsions of liver, spleen and bone marrow and several lymph glands, with second passages, if necessary.

Stage of infection

A further matter of importance is the stage of the infection at which the test of the therapeutic agent should be instituted. Although in the syphilitic rabbit the treatment, when the primary manifestations are fully developed, gives an opportunity of watching and gauging the speed of disappearance of *S. pallida* and of the primary sores themselves I think that sterilization or cure might be more difficult in the latent stage, that is about three to four months after the inoculation. Administration of the remedy then would be a better test. In the syphilitic mouse the treatment should not be started until about two months after the inoculation

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since, according to Prigge (1929), this is the time when the spirochaetes may be expected to be well distributed throughout the mouse's tissues.

Interval between treatment and test of cure

As regards the important factor of the actual length of the interval between treatment and the application of the tests of cure, I think that, for the reasons set out below, it should be not less than one year in rabbits and not less than six to eight months in mice. Chesney and Kemp (1925) thought that an interval of fifty-three days was sufficient as previous experiments had shown them that such time would allow the effects of treatment to wear off. Voegtlin and Dyer (1927) delayed the tissue transfer to normal animals six to twenty weeks in order to give any spirochaetes which had survived the treatment a chance of remultiplying and spreading the infection. That such ideas were not without reason was shown by the results of Prigge's (1928) experiments. Prigge found in six rabbits treated with small doses of Silver-Salvarsan or Neosalvarsan 57 to 159 days after the infection that lymph glands removed 8 to 66 days after treatment were negative, but those removed 151 to 240 days after treatment were infectious. The results of the first negative lymph node transfers were checked up partly by second lymph gland passages. The results of Prigge's experiments, although he used only small doses of arsenobenzol preparations, show that Schlossberger and Worms (1932) were right in lengthening the time interval between treatment (carried out with large doses of Neosalvarsan) and the removal of glands in their own experiments to eleven to twelve months. Such an interval not only gives ample time for excretion of the drugs, but also allows any surviving spirochaetes to recover their virulence. The precaution was also justified by the fact that Schlossberger (1930) had seen in mice results of premature removal similar to those reported by Prigge which have been quoted above. Thus transfers from mice treated with single doses of 1/150 gramme of Neosalvarsan per 20 grammes of body weight, late in the course of the infection, to rabbits a short time after treatment, were negative (transfer of lymph glands, spleen and brain) but those carried out four to six months after treatment were positive.

These few references, which are probably not complete, show that the importance of a suitable time interval between treatment and test by transfer of tissue emulsion has been long recognized by a considerable number of workers. It is certainly a safe procedure, in my opinion, to extend this time interval even longer than six months, perhaps about a year. Eagle, Hogan and Kemp in their paper have discussed the possibility that rabbits with lymph glands free of spirochaetes after six months might show spirochaetes in other lymph glands removed at later periods.

Two exceptional results

Case (1).—The importance of the time factor can be further recognized in two rather exceptional results I noted in the course of my experiments. The first (1926) is the case referred to with some apparent scepticism by Eagle, Hogan and Kemp. Five rabbits infected with the Nichols strain of *S. pallida*, which had produced typical primary lesions in all, were intravenously treated in the latent stage of the infection, 188 to 370 days after inoculation, with Neosalvarsan. In two cases they were given single doses of 200 milligrams per kilo and in three others three doses of 100 milligrams per kilo at weekly intervals. From 6 to 21 days after treatment a popliteal lymph gland of each of these animals was separately transferred to a healthy rabbit (first passage). After an observation time of 109 to 131 days in which none of the first passage rabbits showed any syphilitic manifestation a popliteal lymph gland of each of them was transferred to a healthy rabbit (second passage). One of these second passage rabbits developed a primary syphilitic lesion with numerous *S. pallida*. The originally infected animal was rabbit No. 457. Treatment consisted of three intravenous doses of 100 milligrams of Neosalvarsan per kilo of body weight given at weekly intervals; 188 days after the inoculation and 21 days after treatment its popliteal gland was removed and

transferred to a first passage rabbit ; after the latter had been watched for 109 days, in which it did not show any manifestation, its popliteal gland was removed and transferred to a second passage rabbit. The primary sore which developed in the second passage rabbit eight weeks after inoculation was certainly not due to infection with *S. cuniculi*, as suggested by Eagle, Hogan and Kemp. It was a typical syphilitic primary sore with hard infiltration such as is never seen in cuniculi infections ; I may add that precautions by suitable quarantine were always taken with my experimental animals to exclude cuniculi infection with which I have been familiar for many years. The suggestion of laboratory error which has been made by Eagle, Hogan and Kemp seems regrettable, having regard to the evidence of experience in this work which must have been obvious in the details of the experiments reported upon.

Case (2).—Further, the result was supported by a similar experience reported in collaboration with Schlossberger (1932) and apparently not known to Eagle, Hogan and Kemp. In this paper we had reported the case of rabbit No. 21 which was one of five animals intravenously treated late in the latent stage of the infection with three successive weekly doses of 0.1 gramme of Neosalvarsan per kilo of body weight. From rabbit No. 21 both inguinal glands were removed eleven months and twenty days after the last Neosalvarsan injection and were intratesticularly transferred to two rabbits. One of the pair died but the other showed a typical primary manifestation with abundant *S. pallida* two months and five days after the inoculation. I think the second case a good supplement to the first although, admittedly, both are exceptional. Probably in the first case the short time interval had depressed the spirochaetes still contained in the transferred gland and a second passage was necessary, but in the second case the long period of eleven months and twenty days had given ample time to *S. pallida* to recover its virulence. Alternatively, *S. pallida* from other foci may have penetrated into the gland again and therefore a positive result could be obtained without a second passage. In this connexion it may be useful to recall that Schlossberger (1937) failed to cure late syphilis in mice—at least apparently in a part of his animals—even with doses of Neosalvarsan closely approximating the maximum tolerated dose.

Summary

Summarizing, I would suggest the following for the testing of a chemotherapeutic preparation.

- (1) The preparation under examination should be tried finally not only on syphilitic rabbits but also on syphilitic mice. In rabbits it should be tried in the latent stage after the first outbreak of active symptoms, i.e. about three to four months after infection, and in mice not less than two months after the inoculation, when the infection of the central nervous system has been well established.
- (2) The test by tissue transfer should be performed in rabbits not less than one year after the treatment, and during the year the rabbits should be closely watched for any sign of recurrence. In mice the test should be made in not less than six to eight months after treatment.
- (3) For the transfer the material should be used as follows. (a) Emulsion of a mixture of spleen, liver, marrow of several bones and testes of the treated rabbits ; (b) emulsion of several lymph glands of the treated rabbit ; (c) emulsion of whole organs (including brain, which should be transferred separately) and of several lymph glands of the treated mouse.

Some of the rabbit tissue emulsions and, if possible, the whole of each of the mouse emulsions, should be inoculated into a series of three or four rabbits. The inoculated rabbits should be watched for five months and in the event of none showing any sign of syphilitic infection a second passage of emulsion of testes, other organs and lymph glands of the inoculated rabbits should be made into a further series of rabbits, which in turn should be watched for three to five months.

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Admittedly this is all troublesome* but it is only by such thoroughness in testing that the inherent fallacies in the transfer method can be minimized ; the trouble, time and expense are justified when a judgment of the value of a chemotherapeutic preparation depends on the result.

(I am again greatly indebted to Colonel Harrison for his kind revision of the text of this paper.)

* A suggestion to shorten the time necessary for testing the sterilizing power of a chemotherapeutic agent was made by G. E. Wakerlin and A. S. Loevenhart (1928). Referring to the results of S. S. Greenbaum and M. J. Harkins (1924) they recommended "the determination of prophylactic ability" as "an addition to the technique employed in the therapeutic study of compounds in experimental syphilis". T. F. Probe (1933) somehow confirmed the results of Greenbaum and Harkins as well as those of Wakerlin and Loevenhart, which these authors had obtained with neoarsphenamine, in the preventive treatment of syphilitic rabbits. He found that "it requires approximately the same dose of neoarsphenamine, administered two days after the inoculation, to protect rabbits against the development of the disease as is needed to cure rabbits of the infection when treatment is delayed until two months after inoculation or until late in the active stage of the infection". This work requires further examination.

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Prevalence of syphilis among men of draft age

According to an analysis made by R. A. Vonderlehr and Lida J. Usilton of 1,895,778 serological reports of men of draft age (21-35) in the United States of America the rate of prevalence of syphilis amongst selectees is 45.3 per thousand. The rate for the entire male population in the same age group is estimated to 47.7 per thousand. The rate of prevalence among Negro selectees is 252.3 per thousand, and among white selectees 17.4 per thousand. The estimated rate of prevalence for the entire male Negro population aged twenty-one to thirty-five is 272 per thousand compared with that for the entire male white population of 23.5 per thousand.

Among selectees from rural areas the prevalence rate of syphilis is 43.8 per thousand, from urban areas 46.1 per thousand. Highest rates, white and Negro, are found in the South-eastern states.—(*Journal of the American Medical Association*, (1942) **120**, 1369.)

